Paper No. 20

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte RICHARD G. LANZARA

Appeal No. 2001-1437
Application No. 08/764,145

ON BRIEF

Before SCHEINER, MILLS and GRIMES, Administrative Patent Judges,

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-5 which are the claims pending in this application.

Claim 1 is representative of the claims on appeal and reads as follows.

1. A formulation that elicits a desired response from cellular receptors and prevents subsequent desensitization of said receptors comprising an agonist suitable for eliciting said response in a first amount effective for binding to said receptors in both a high and a low affinity state effective for obtaining said response mixed with an inhibitor of said agonist specific to said receptors, said inhibitor in a second amount sufficient to prevent desensitization of said receptor, said second amount being $K_i(K_{DL}K_{DH}/2)$-½ of said first amount, where K_{DL} and K_{DH} are dissociation constants of said agonist in low and high affinity states, respectively, and K_i is the dissociation constant of said inhibitor.

The references relied upon by the examiner are:

Geoffroy, M. et al. (Geoffroy), "Reduction of Desensitization of a Glutamate Ionotropic Receptor by Antagonists," Molecular Pharmacology, Vol. 39, pp. 587-591 (1991)

Fernandes, L.B., et al. (Fernandes), "β-Adrenoceptor desensitization in guinea-pig isolated trachea," European Journal of Pharmacology, Vol. 15, pp. 135-145 (1988)

Grounds of Rejection

Claims 1-5 stand rejected under 35 U.S.C. § 102(b) as anticipated or in the alternative under 35 U.S.C. § 103(a) as obvious in view of Geoffroy.

Claims 1-5 stand rejected under 35 U.S.C. § 102(b) as anticipated or in the alternative under 35 U.S.C. § 103(a) as obvious over Fernandes.

We reverse these rejections.

DISCUSSION

In reaching our decision in this appeal, we have given careful consideration to the appellant's specification and claims, to the applied prior art references, and to the respective positions articulated by the appellant and the examiner.

Rather than reiterate the conflicting viewpoints advanced by the examiner and the appellant regarding the above-noted rejection, we make reference to the Examiner's Answer for the examiner's complete reasoning in support of the rejection, and to the appellant's Brief and Reply Brief for the appellant's arguments thereagainst. As a consequence of our review, we make the determinations which follow.

Background

Appellant "solve[s] the problem of determining the optimal concentration of an antagonist or inhibitor which is necessary to prevent cellular receptor desensitization without causing unnecessary or unwanted inhibition." Specification, page 5. Appellant prepares a "formulation [which] combines a competitive antagonist with an agonist for/of a particular receptor in a specific proportion that maximizes the receptor response to the agonist and maintains this maximum response. This formulation describes precisely the concentration of the antagonist relative to that of the agonist." Specification, pages 5-6.

Thus, appellant claims a formulation (composition) that elicits a desired response from cellular receptors and prevents subsequent desensitization of said receptors. The formulation includes an agonist suitable for eliciting said response in a first amount

effective for binding to said receptors in both a high and a low affinity state effective for obtaining said response mixed with an inhibitor of the agonist specific to the receptors. The inhibitor of the agonist specific to the receptors is in a second amount sufficient to prevent desensitization of the receptor, the second amount being $K_i(K_{DL}K_{DH}/2)$-½ of the first amount, where K_{DL} and K_{DH} are dissociation constants of said agonist in low and high affinity states, respectively, and K_i is the dissociation constant of said inhibitor.

It follows that once the first drug or agonist has been selected and its dosage amount chosen, this leads to a specific amount of drug for the inhibitor of the agonist in the formulation of the claims. According to the specification, the "instant formulation determines the lowest acceptable dose of inhibitor or antagonist to mix with the drug which completely prevents desensitization." Specification, page 13.

35 U.S.C. § 102(b)/103(a)

Claims 1-5 stand rejected under 35 U.S.C. § 102(b) as anticipated or in the alternative under 35 U.S.C. § 103(a) as obvious in view of Geoffroy.

To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either explicitly or inherently. In re Schreiber, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed. Cir. 1997). A prima facie case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. In re Bell, 991 F.2d 781, 783, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993). An obviousness analysis requires

that the prior art both suggest the claimed subject matter and reveal a reasonable expectation of success to one reasonably skilled in the art. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

According to the examiner, "Geoffroy teaches addition of different concentrations of antagonist to agonist resulting in changing the degree of receptor desensitization .... If the ratio of antagonist to agonist shown in Figure 4 does not represent the optimum ratio, then it would have been obvious to one of ordinary skill in the art to continue the process of Geoffroy et al. and to arrive at the optimum ratio for combining agonist and antagonist to achieve the desired results because optimization of results is routine procedure and within ordinary skill." Answer, page 4. As to the requisite expectation of success, the examiner finds that (Answer, pages 4-5):

> One would reasonably expect to be successful in determining the optimum agonist:antagonist ratio experimentally because Geoffroy shows an effective experimental system to use as well as the dose dependence of the effects of agonist and antagonist within that system... Optimum concentrations of agonist and antagonist to be used within a system to achieve a known and demonstrated result represent the same composition, regardless of the method used to determine the amounts of each. It is believed that because the relevant effect is demonstrated, the claimed composition ratio must have been achieved and thus the claimed composition is anticipated. If not, it would have been obvious to continue the empirical method taught by Geoffroy to determine more precisely what the optimum ratio is and one would have expected success in doing so because Geoffroy shows the dose dependence of the observed effect.

In rebuttal, appellant argues that the claimed "precise formulation is not disclosed textually or inherently" by Geoffroy. Brief, page 3. Appellant argues that the conclusion that the examiner draws that Geoffroy shows the claimed formula (inherently) because

they show an agonist to antagonist ratio that effects resensitization, "is not true." Id.

Appellant argues (Brief, pages 3-4):

> [b]y the very nature of their experimental sampling, with *normalization* of these data, Geoffroy *et al.* were prevented from, literally rendered incapable of, even observing the optimal agonist-antagonist ratio... Geoffroy *et al.* do not show observed or inherent data points for the precise titration of antagonist, that is, the critical point or optimal formulation of the appellant's invention. Were such the case, their response curve (Fig. 6) would show clearly a sustained (flattened) response. Instead, and contrary to appellant's results, their Fig. 6 indicates a desensitization.

With respect to the obviousness rejection, appellant further argues "the position that Geoffroy *et al.* were merely operating within a range near appellant's optimal results is irrelevant in that without some foreknowledge of what to look for, one of ordinary skill in the art would have to be content with their limited data and conclusions, neither of which could impel a routineer to make the instant invention." Brief, pages 4-5.

The examiner responds, arguing that "the instant claims are drawn to a formulation and not to an explanation or a model that would result in the claimed formulation. The existence of an agonist:antagonist composition that effects receptor resensitization is deemed to anticipate the claimed compositions, in the absence of factual evidence that the prior art composition is any different from the one claimed." Answer, page 6.

While we find merit in the examiner's observation that the claimed invention is directed to a formulation or composition comprised of specific amounts of ingredients not to a formula or explanation that would result in the claimed formulation, we agree

with appellant that the examiner has failed to establish with sufficient evidence, a prima facie case of anticipation and/or obviousness. What is missing from the examiner's analysis is a specific indication of where the cited reference describes a specific formulation which includes a specific amount of inhibitor to prevent desensitization of a receptor in relation to a specific amount and type of drug administered (the lowest acceptable dose of inhibitor or antagonist to mix with the drug which completely prevents desensitization). We disagree with the examiner's conclusion that because the principle of desensitization is generically disclosed in Geoffroy, in particular the dose dependence of the effects of agonist and antagonist upon desensitization, that this would have directed one of ordinary skill in the art specifically to an optimum amount of antagonist to prevent desensitization of a specific amount of the specific drug chosen.

In his rebuttal argument appellant tries to elucidate this point, arguing that "none of the references in the case disclose any fact or notion that a cellular receptor can be "immunized" against desensitization from the inception of delivery of the agonist-antagonist formulation. Clearly no precise formulation having this attribute nor the continuing maximal cellular responsiveness, as claimed, is disclosed or even intimated." Reply Brief, pages 3-4.

Appellant argues (Reply Brief, page 6):

> The probability of selecting a point representing the optimum ratio of agonist to antagonist is vanishingly small because there are an infinite number of points on a line. To find the precise point, as in applicant's

> formula, undue and exhaustive experimentation would be required. Most importantly, the data used for each point were NORMALIZED and are in disagreement by about one order of magnitude (0.2 vs. 0.005). Thus, the two points from the curves, in the presence of DNQX, and upon which the Examiner relies as being at or near to the maximum of the control curve (without DNQX) ARE NOT TRUE MAXIMA because of the nature of their random selection of points together with the presentation of only data that had been normalized. These facts clearly demonstrate that the investigators DID NOT, NOR COULD NOT derive the claimed formulations that would provide the unique attributes of this invention. [Emphasis in original.]

Responding to the appellant, the examiner maintains the argument that optimization of a result (desensitization) effective variable (concentration of the antagonist) is routine in the absence of unexpected results. Answer, page 9. While we agree with the examiner that "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art," In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980) (citations omitted), our reviewing court has found an exception to this general rule where "the parameter optimized was not recognized to be a result effective variable," In re Antonie, 559 F.2d 618, 621, 195 USPQ 6, 8 (CCPA 1977).

In our view, the examiner has not established that one of ordinary skill in the art would have been able to determine an optimum dosage of agonist and antagonist to prevent desensitzation altogether, from the general principle of the dose (concentration) dependence of desensitization. There is no compelling evidence of record that the relevant effect was achieved by the prior art. The examiner has not established that the reference describes a formulation having the specifically claimed amounts of

antagonist and agonist. Stated differently, the examiner has failed to establish that the recognized dose dependence of the effects of agonist and antagonist upon desensitization alone described in Geoffroy, is a result effective variable which would have directed one of ordinary skill in the art specifically to the claimed optimum amounts of agonist and antagonist to prevent desensitization of the drug (agonist). Appellant argues that selection of the claimed formulation is based, in part, on the parameter of the dissociation constants of the agonist and antagonist of the receptor involved which are not parameters recognized in Geoffroy to be result effective.[1]

In our view, the examiner has failed to provide an indication of specific evidence, or appropriate argument under the principles of In re Best, in the first instance, to shift the burden to appellant to establish that a prior art product does not necessarily possess the characteristics of the claimed product when the prior art and claimed products are identical or substantially identical. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 432 (CCPA 1977).

Appellant has argued that the claimed maximum critical point is not disclosed or described in Geoffroy and could not be derived from the reference. The examiner has failed to rebut this argument.

In view of the above, the rejections of the claims over Geoffroy are reversed.

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[1] See also other relevant parameters, specification, pages 15-23.

35 U.S.C. § 102(b)/103

Claims 1-5 stand rejected under 35 U.S.C. § 102(b) as anticipated or in the alternative under 35 U.S.C. § 103(a) as obvious over Fernandes.

According to the examiner, "Fernandes demonstrates the effect of β-adrenoreceptor antagonists on isoprenaline-induced desensitization of guinea pig trachea in which isoprenaline is present at 25μM and an antagonist (either CI118551 or propanolol) is present at 0.2μM... The agonist-antagonist compositions are believed to anticipate the claimed compositions because reversal of desensitization is demonstrated as shown in Table 4 and because the ratio of antagonist:agonist falls within the range of about 10^{-1} to about 10^{-6}, but if not, it would have been obvious to optimize the amounts of antagonist and agonist in order to achieve the desired effect of reversing desensitization." Answer, pages 6-7.

Appellant argues Fernandes fails to disclose the claimed formula, and that the experimental data are not sufficient for showing or readily deriving a precise and critical value for the claimed desensitization-preventing agonist and antagonist optimum ratios as claimed. Brief, page 6. "Most significantly, like Geoffroy *et al.*, Fernandes *et al.* are completely silent on the physiochemical parameters (K_i, K_{DH}, K_{DL}), which the routineer in the art should or could use to determine a precisely optimum ratio." Brief, pages 7-8. Furthermore, appellant argues that "appellant's method (U.S. Pat. No. 5,597,699) shows that the propanolol dose, reported by Fernandes *et al.* to be sufficient for reduction of

desensitization, is not sufficient to optimize it to the maximal response level." Brief, page 7.

We remind the appellant, as did the examiner, that the subject matter of the present claims is a specific formulation, and undue attention need not be directed at how, or by what formula, the specific formulation was derived, when comparing the claimed formulation to compositions found in the prior art.

We do not, however, find the examiner has established a prima facie case of anticipation or obviousness by providing evidence in the prior art of a formulation representing an optimum amount of antagonist to prevent desensitization of a specific amount of the drug (agonist).

The rejections of the claims in view of Fernandes are reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

REVERSED

TONI R. SCHEINER Administrative Patent Judge	)
	) BOARD OF PATENT
DEMETRA J. MILLS Administrative Patent Judge	) APPEALS AND
	) INTERFERENCES
ERIC GRIMES Administrative Patent Judge	)

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